

# Reduction of Operative Morbidity and Mortality by Combined Preoperative and Postoperative Nutritional Support

JAMES L. MULLEN, M.D., GORDON P. BUZBY, M.D., DAVID C. MATTHEWS, M.D., BRIAN F. SMALE, M.D., ERNEST F. ROSATO, M.D.

A previously developed and validated predictive nutritional assessment model (Prognostic Nutritional Index) was applied to a heterogeneous surgical population. Without knowledge of the then undeveloped PNI, adequate preoperative nutritional repletion (TPN) was provided on clinical indications alone to 50 of 145 patients with the remaining 95 patients receiving no preoperative total parenteral nutrition. Analysis of the two groups found no baseline differences in nutritional status, type and severity of disease and/or operative therapy, and other potentially important variables. In the high-risk stratified group as defined by admission nutritional assessment and calculated PNI ( $\geq 50\%$ ), adequate preoperative TPN reduced postoperative complications 2.5-fold ( $p < 0.01$ ), postoperative major sepsis six-fold ( $p < 0.005$ ) and mortality five-fold ( $p < 0.01$ ). Clinical "eyeball" evaluation of nutritional status cannot identify high-risk individuals. This nutritional assessment predictive model (PNI) identifies the subset of operative candidates in whom adequate preoperative nutritional support significantly reduces operative morbidity and/or mortality.

*From the Departments of Surgery,  
University of Pennsylvania School of Medicine and  
the Philadelphia Veterans Administration Medical Center,  
Philadelphia, Pennsylvania*

regardless of the status of their gastrointestinal tract or the presence of complicating metabolic disorders. Preoperative total parenteral nutrition, however, is not without potential disadvantages including prolongation of hospital stay, increased cost of hospitalization, and its own inherent minimal morbidity. Prerequisite to rational use of preoperative parenteral nutritional support are several important premises: 1) protein-calorie malnutrition (PCM) must be accurately and objectively defined in the clinical setting; 2) PCM must lead to increased operative morbidity and/or mortality rates or to decreased patient response to operative therapy; 3) a reliable method to quantitate the risk of a nutritionally-based complication in an individual patient must be available to allow the surgeon to assess the risk of delaying surgery for preoperative nutritional repletion against the risk of immediate surgery in the presence of untreated PCM; 4) preoperative nutritional support of the malnourished patient must result in decreased morbidity and/or mortality to the level achieved in the well-nourished operative candidate or must produce an increased response to surgery. Recent studies from this institution<sup>5,30,31,37</sup> and others<sup>22,27</sup> have provided objective data to satisfy the first three of these four prerequisites. Despite extensive use of preoperative parenteral nutritional support and a strong clinical impression that it is a valuable therapeutic modality, conclusive objective documentation of its efficacy in reducing operative morbidity and/or mortality is lacking.

This report is the third phase of an ongoing effort at this institution investigating the interrelationship between protein-calorie malnutrition and operative

RECENT SURVEYS HAVE DEMONSTRATED an alarming incidence of malnutrition in hospital patients.<sup>2,25,30</sup> Numerous studies have demonstrated a positive correlation between abnormalities in various objective measures of nutritional status and increased operative morbidity and mortality in surgical patients.<sup>22,27,30</sup> This increased awareness of the prevalence and consequences of untreated protein-calorie malnutrition has provided a strong clinical incentive for the aggressive nutritional support of malnourished patients. Refinement and sophistication of techniques for parenteral nutrient administration have made optimal nutritional support possible in virtually all patients

Presented in part at the Fourth Tripartite Meeting, Oxford, England, July 5-7, 1979.

Reprint requests: James L. Mullen, M.D., Hospital of the University of Pennsylvania, 4 Silverstein, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

Supported in part by Educational Grants from McGaw Laboratories, the McCabe Fund, Cutter Laboratories, and Veterans Administration Medical Research Funds.

Submitted for publication: March 4, 1979.

morbidity and/or mortality. In phase I, measures of nutritional status which are statistically related to increased operative morbidity and/or mortality were identified.<sup>30</sup> That study and others<sup>22,27</sup> have provided an objective definition of "*clinically significant malnutrition*" in surgical patients (*i.e.*, nutritional deficits which when present are associated with increased operative morbidity). Although statistically valid for large patient populations, these studies do not permit prediction of operative risk in an individual patient. In phase II an "index" of nutritional status was developed<sup>31</sup> and prospectively validated.<sup>5,37</sup> This index (Prognostic Nutritional Index) does permit such a quantitative prediction of operative risk based on admission nutritional status as measured by a battery of nutritional studies.

The purpose of this phase III study was to investigate the efficacy of optimal preoperative nutritional support in reversing PCM and decreasing morbidity and/or mortality rates in the malnourished surgical patient. The specific objectives were: 1) to further test the validity and clinical applicability of the Prognostic Nutritional Index (PNI) in predicting complications based on admission nutritional status in a heterogenous group of surgical patients; 2) to determine if preoperative nutritional support is effective in reducing operative morbidity and/or mortality in this heterogenous population or in some specific subset of this population; and 3) to determine if the PNI may be useful in the identification of which subset of patients, if any, will benefit from preoperative nutritional support.

### Materials and Methods

All patients referred to the Nutrition Support Service of the Hospital of the University of Pennsylvania for nutritional assessment during the period January 1, 1978 through June 30, 1978, were eligible for this study. Entry criteria were as follows:

- 1) Complete preoperative nutritional assessment data available.
- 2) Preoperative nutritional support technically and medically feasible.
- 3) Delay in surgery for preoperative nutritional support not clinically contraindicated.
- 4) Patients received either:
  - a) Adequate preoperative nutritional support
    - i) >7 days
    - ii) >35 kcal/kg/day
    - iii) >1.5 g protein/kg/day.
  - b) no preoperative nutritional support.
- 5) Clinical decision regarding use of preoperative TPN was made before the availability of PNI predictive data.

- 6) Patients underwent a major intra-abdominal or intrathoracic operative procedure.
- 7) Clinical course adequately documented until death or discharge.

One hundred forty-five patients met these criteria and comprise the study population.

Within 24 hours of referral to the Nutrition Support Service, patients underwent nutritional assessment including variables of personal data (age, sex, race and diagnosis) and variables of nutritional status including anthropometrics (triceps skinfold, mid-arm muscle circumference, body weight, degree of weight loss, rate of weight loss), measures of secretory protein status (total serum protein, serum albumin, and serum transferrin) and measures of immunologic function (total lymphocyte count, delayed hypersensitivity reactivity). A description of the techniques used in these measurements have been presented elsewhere.<sup>30</sup> All patients underwent a major intra-abdominal or intrathoracic surgical procedure and their clinical course was monitored for objective complications until death or discharge by an observer with no patient-care responsibilities and no knowledge of their baseline nutritional studies (GPB). Complications monitored included: death, septicemia, intra-abdominal abscess, wound infection, wound dehiscence, fistula formation, urinary tract infection, pneumonia, congestive heart failure, phlebitis, respiratory insufficiency, pulmonary embolus, cerebrovascular accident, and shock. Rigid objective criteria were established defining each complication to avoid subjective observer bias. A diagnosis of septicemia required a positive blood culture associated with hypotension and hypoperfusion. An intra-abdominal abscess was defined as an intra-abdominal purulent collection requiring operative drainage. Fistulae were radiographically documented. A diagnosis of urinary tract infection required a quantitative culture of greater than 100,000 organisms. Pneumonia was documented by an abnormal chest x-ray, positive sputum culture, and treatment with antibiotics. The presence of a wound infection required documentation by culture and operative or spontaneous drainage of purulent material. A wound dehiscence required operative reclosure of the wound. Phlebitis was documented by venographic studies and was treated with heparin. Congestive heart failure was diagnosed by standard clinical and radiologic criteria and required treatment with digitalis and diuretics. Respiratory failure implied the need for ventilatory assistance for more than six hours after surgery. Pulmonary embolus was demonstrated by lung scan or pulmonary angiography and was treated with heparin. A cerebrovascular accident was documented by a new and persistent neurologic

TABLE 1. IVH Formula

	Content per 1000 ml
Dextrose	250 g
Amino acids (McGaw, Freamine II)	39 g
NaCl	0–40 mEq
Na acetate	0–30 mEq
KHPO <sub>4</sub>	10 mEq
Ca gluconate	4.8 mEq
MgSO <sub>4</sub>	8 mEq
MVI (USV)*	5 cc
Folate (Lederle, Folvite)*	5 mg

\* Added to first bottle daily only.

deficit. A diagnosis of shock required hypotension, hypoperfusion, and treatment with systemic vasopressors.

To determine if baseline nutritional studies can be used to prospectively identify which subset of surgical patients may benefit from preoperative nutritional support, patients were retrospectively stratified according to admission nutritional status using a previously developed<sup>31</sup> and validated<sup>5,37</sup> linear predictive model. This predictive model relates risk of operative morbidity and/or mortality to nutritional status and is given by the relation: Prognostic Nutritional Index (%) = 158 – 16.6 (ALB) – 0.78 (TSF) – 0.20 (TFN) – 5.8 (DH) where “Prognostic Nutritional Index” (PNI) is the risk (per cent) of a complication occurring in an individual patient, “ALB” is serum albumin level (grams per decaliter), “TSF” is triceps skinfold (millimeters), “TFN” is serum transferrin level (milligrams per decaliter), and “DH” is cutaneous delayed hypersensitivity reactivity to any of three recall antigens (mumps, SKSD, Candida) graded as 0 (non-reactive to all antigens), 1 (<5 mm induration to one or more antigens) or 2 (>5mm induration to one or more antigens). For all study patients the PNI was calculated based on initial preoperative assessment data. An example of the calculation of the PNI in a hypothetical well-nourished patient is shown in the footnote below.\*

Most patients (93%) received parenteral nutritional support at some time during the preoperative (34%)

\* Calculation of prognostic nutritional index (PNI) in a hypothetical well-nourished patient.

$$\text{PNI} = 158\% - 16.6(\text{ALB}) - 0.78(\text{TSF}) - 0.2(\text{TFN}) - 5.8(\text{DH})$$

$$\text{Albumin} \rightarrow 4.8 \text{ g/dl} \times 16.6 = 79.7$$

$$\text{Triceps skinfold} \rightarrow 14 \text{ mm} \times 0.78 = 10.9$$

$$\text{Transferrin} \rightarrow 250 \text{ g/dl} \times 0.20 = 50.0$$

$$\text{Skin test reactive} \rightarrow 2 \times 5.8 = 11.6$$

$$\text{Total} = 152.2$$

$$\text{PNI} = 158\% - 152\% = 6\%$$

Predicted risk of complications in this patient is 5.8%.

and/or postoperative (93%) period. All patients who received preoperative parenteral nutrition also continued to receive TPN during the postoperative period. The decision to initiate nutritional support was made by the primary surgeon on clinical grounds alone since the Prognostic Nutritional Index data was not developed or available during the time period of their hospitalization. The composition of intravenous hyperalimentation fluid is shown in Table 1. During total parenteral nutrition patients received 1000  $\mu\text{g}$  of vitamin B<sub>12</sub> intramuscularly on the first day of intravenous feeding and 10 mg of vitamin K, twice a week, but received no iron or trace metal supplements. Fat supplementation was initiated on the fifteenth day of total parenteral nutrition. Patients were administered 500 cc of 10% soybean emulsion twice a week. Patients with functional gastrointestinal tracts were permitted to eat unless clinically contraindicated. Daily intake of fluids, calories, and protein (intravenous and by mouth) were reported for each patient.

TABLE 2. Patient Population Characteristics vs Preoperative and No Preoperative TPN

	Preoperative TPN	No Preoperative TPN
Number	50	95
Age (mean $\pm$ SEM)	55.0 $\pm$ 2.46(SEM)	59.6 $\pm$ 1.45
Nutritional Status (% of patients)		
PNI < 40%	36%	34%
PNI = 40–49 (%)	20%	19%
PNI ( $\geq$ 50)	44%	47%
Sex (males/females)	20/30	47/48
Diagnosis (% of patients)		
cancer (all sites)	56.0	52.6
colon primary	14.0	18.9
pancreas primary	8.0	8.4
stomach primary	6.0	6.3
esophagus primary	4.0	4.2
small bowel primary	0	1.1
bladder/urethra		
primary	12.0	6.3
kidney primary	0	2.1
prostate primary	2.0	0
cervix/endometrium		
primary	4.0	1.1
ovary primary	2.0	2.1
head and neck primary	2.0	0
lymphoma primary	2.0	2.1
nonmalignant bowel		
obstruction	2	9.5
nonmalignant biliary		
obstruction	2	3.2
ulcerative colitis	4.0	3.2
regional enteritis	10.0	3.2
peptic ulcer disease	6.0	4.2
diverticulitis	8.0	3.2
morbid obesity	0	6.3
vascular disease	2.0	3.2
enterocutaneous fistula	6.0	2.1
other	4.0	9.5
Preoperative TPN	100%	0%
Postoperative TPN	100%	89%

TABLE 3. *Complications vs Preoperative and No Preoperative TPN*

	Preoperative TPN	No Preoperative TPN
Septic complications		
urinary tract infection	0	1
wound infection	3	3
Major septic complications		
septicemia	1	12
intra-abdominal abscess	1	9
pneumonia	1	6
Nonseptic complications		
respiratory insufficiency	1	9
shock	1	6
wound dehiscence	0	1
fistula	1	3
cerebrovascular accident	0	1
pulmonary embolus	0	2
phlebitis	1	1
Total	10 in 9 pts.	54 in 37 pts.

### Results

All 145 patients (67 males, 78 females; mean age  $58.0 \pm 1.28$  SEM) were available for follow-up study through their hospital course.

Fifty patients (34.5%) received at least seven days of "adequate" preoperative nutritional support ( $>35$  kcal/kg/day,  $>1.5$  g protein/kg/day), and 95 patients (63.5%) received no preoperative support although several underwent central venous catheter placement prior to surgery in anticipation of postoperative support. The two study groups (preoperative TPN vs no preoperative TPN) were similar in terms of age, sex distribution, admission nutritional status, and underlying disease process as shown in Table 2.

Complications observed are given in Table 3. A total of 64 complications occurred in 46 patients (31.7%), and there were 29 deaths (20.0%). Many of these complications were due to infection (58%) and some could be related to muscle weakness and/or prolonged immobilization (respiratory insufficiency, phlebitis). Ten complications occurred in nine patients who received preoperative TPN (18.0%) and there were two deaths (4.0%). Fifty-four complications occurred in 37 patients who did not receive preoperative TPN (38.9%) and there were 27 deaths (29.4%). These large differences in the morbidity and mortality rates are significant by chi square analysis ( $p < 0.01$  for complications;  $p < 0.005$  for mortality).

The distribution of patients and complications according to Prognostic Nutritional Index are given in Figure 1. The distribution of patients approximates a bell-shaped curve, but the incidence of complications increases linearly with increasing PNI. Comparison of the incidence of complications (Fig. 2a) and death (Fig. 2b) as a function of PNI in supported and nonsupported patients demonstrates that preoperative nutritional support effectively produces a "shift to the right" in these curves. Patients were stratified into high risk ( $\text{PNI} \geq 50\%$ ) intermediate risk ( $\text{PNI } 40\text{--}49\%$ ), or low risk ( $\text{PNI} < 40\%$ ) groups. The characteristics of the three risk groups are shown in Table 4. All three groups were similar in terms of mean age, sex distribution, diagnosis, and use of preoperative nutritional support. Actual complications observed in each group are given in Table 5. To permit statistical comparison by chi square analysis, individual complications were classified into four groups; death, any

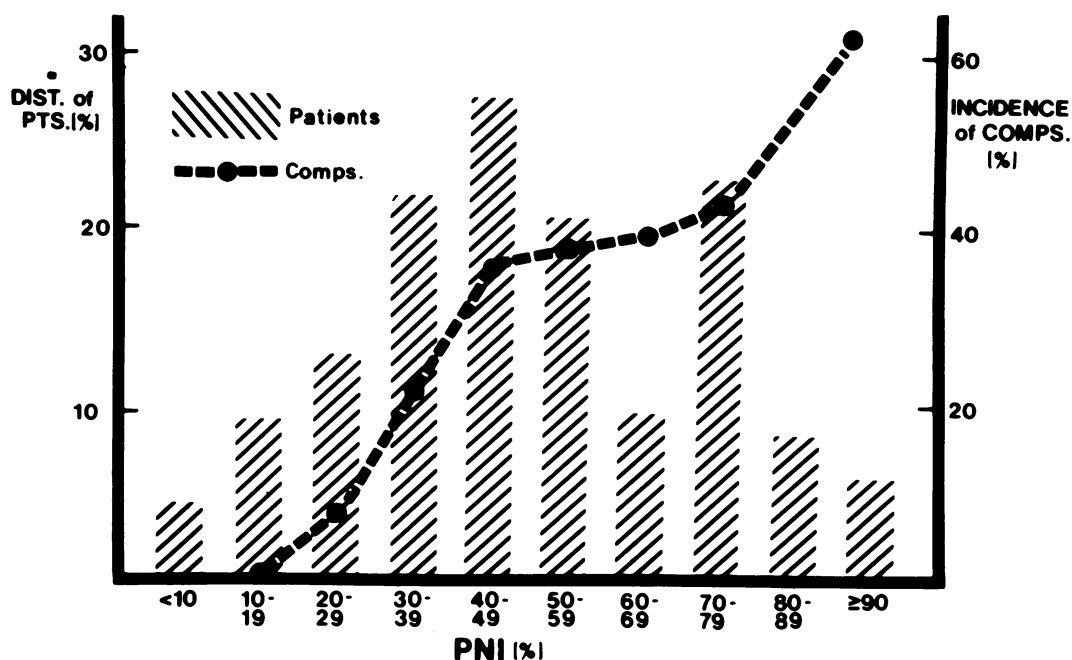


FIG. 1. Distribution of patients and complications according to Prognostic Nutritional Index (PNI). The distribution of patients approximates a bell-shaped curve while the incidence of complications increases linearly with increasing PNI.

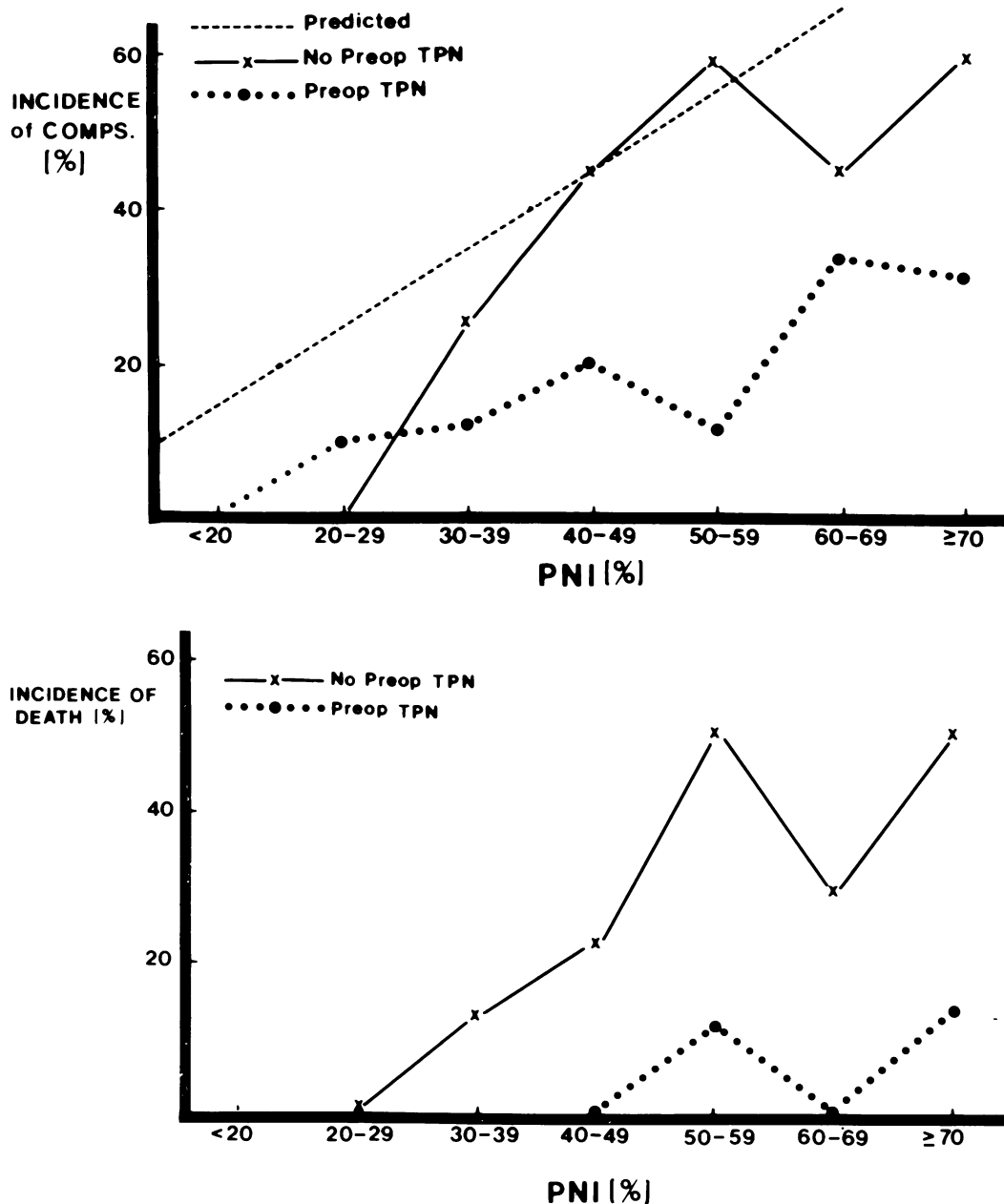


FIG. 2a and b. Incidence of complications (a, top) and death (b, bottom) versus Prognostic Nutritional Index (PNI). In patients who received preoperative TPN and in patients who received no preoperative TPN the incidence of complications and death increase with increasing PNI. In patients who received no preoperative TPN the incidence of complications approaches that predicted by the Prognostic Nutritional Index. The effect of preoperative TPN is to shift the curves for both complications and death downward and to the right.

complication, septic complications (any complication caused by infection), and major septic complications (pneumonia, intra-abdominal abscess, septicemia). Within each risk group the incidence of each class of complications was determined for patients who received preoperative TPN versus those who did not receive preoperative TPN. Results are shown in Table 6. A significant increase in the *actual* incidence of death ( $p < 0.005$ ), complications ( $p < 0.005$ ), sepsis ( $p < 0.0025$ ), and major sepsis ( $p < 0.025$ ) were noted as *predicted* risk (PNI) increased when all study patients were examined as a group. When outcome was compared for patients who received preoperative TPN

relative to those who received no preoperative TPN, a difference was demonstrated only for those patients identified as "high risk" ( $PNI \geq 50\%$ ) by the predictive model. In this high risk group, preoperative nutritional support produced a two and one-half-fold reduction in complications ( $p < 0.01$ ), a seven-fold reduction in major sepsis, ( $p < 0.05$ ) and a five-fold reduction in mortality ( $p < 0.01$ ).

### Discussion

The use of total parenteral nutrition in surgical patients has gradually increased since the development

TABLE 4. Patient Population Characteristics vs Predicted Risk Group

	Low Risk (PNI < 40%)	Intermediate Risk (PNI 40–49%)	High Risk (PNI > 50%)	Total (PNI = 0–100%)
Number	50	28	67	145
Age (mean $\pm$ SEM)	54.9 $\pm$ 2.05(SEM)	57.6 $\pm$ 3.44	60.2 $\pm$ 1.75	58.0 $\pm$ 1.28
Sex (males/females)	23/27	14/14	30/37	67/78
Preoperative nutritional support (%)	36	36	33	
Diagnosis (% of patients)				
cancer (all sites)	56.0	53.6	52.2	53.8
colon primary	16.0	14.3	19.4	17.2
pancreas primary	14.0	7.1	4.5	8.3
stomach primary	4.0	14.3	4.5	6.2
esophagus primary	2.0	10.7	3.0	4.1
small bowel primary	2.0	0	0	0.7
bladder/urethral primary	12.0	7.1	6.0	8.3
kidney primary	2.0	0	1.5	1.4
prostate primary	0	0	1.5	0.7
cervix/endometrium primary	0	0	4.5	2.1
ovary primary	2.0	0	3.0	2.1
head and neck primary	0	0	1.5	0.7
lymphoma	2.0	0	3.0	2.1
nonmalignant bowel obstruction	6.0	7.1	7.5	6.9
nonmalignant biliary obstruction	0	3.6	4.5	2.8
ulcerative colitis	0	14.3	1.5	3.4
regional enteritis	4.0	3.6	7.5	5.5
peptic ulcer disease	6.0	3.6	4.5	4.8
diverticulitis	2.0	3.6	7.5	4.8
morbid obesity	10.0	0	1.5	4.1
vascular disease	4.0	3.6	1.5	2.8
enterocutaneous fistula	4.0	3.6	3.0	3.4
other	8.0	3.6	9.0	7.6

of intravenous hyperalimentation in 1968 by Dudrick et al.<sup>14</sup> at the University of Pennsylvania. Initially, hyperalimentation was reserved as a “last resort” for use in patients in whom there was no available alternative form of treatment. Improvements in nutrient solutions, equipment, and techniques of administration have made total parenteral nutrition technically feasible and relatively safe even in immunologically compromised patients.<sup>9</sup> The recent development of parenteral nitrogen sources with amino acid profiles tailored to improve the metabolic derangements associated with various specific disease states such as renal failure<sup>1,15</sup> and hepatic failure<sup>17</sup> may permit optimal nutritional management of even these difficult patients.

The efficacy of total parenteral nutrition is well-documented in the long-term management of patients who have insufficient small-bowel for adequate absorption of enteral nutrients<sup>4,34</sup> and in providing short-term “bowel rest” in patients with inflammatory bowel disease<sup>16,29</sup> or enteric fistulas.<sup>26</sup> Substantial evidence now exists that total parenteral nutrition may increase patient tolerance and perhaps response to nonoperative treatment of malignant disease.<sup>10,12,18,35</sup> In contrast, the value of parenteral nutrition as an adjunct to the operative treatment of various diseases

has not been as clearly and objectively established. Despite ten years of clinical experience with total parenteral nutrition and a strong impression of its value among surgeons, the efficacy of preoperative nutritional support in reducing operative morbidity and

TABLE 5. Complications vs Stratified Predicted Risk Group

	Predicted Risk Group			
	Low Risk	Intermediate Risk	High Risk	Total
Septic complications				
urinary tract infection	0	0	1	1
wound infection	1	3	2	6
Major septic complications				
septicemia	1	1	11	13
intra-abdominal abscess	2	2	6	10
pneumonia	1	0	6	7
Nonseptic complications				
respiratory insufficiency	1	2	7	10
shock	0	1	6	7
wound dehiscence	0	1	0	1
fistula	1	0	3	4
cerebrovascular accident	0	0	1	1
pulmonary embolus	0	0	2	2
phlebitis	1	1	0	2
Total	8 in 6 pts.	11 in 10 pts.	45 in 30 pts.	64 in 46 pts.

TABLE 6. Actual Outcome vs Use of Preoperative TPN and No Preoperative TPN within PNI Stratification

	Nutritional Stratification							
	All Patients		Low Risk		Int. Risk		High Risk	
	TPN	No TPN	TPN	No TPN	TPN	No TPN	TPN	No TPN
n	50	95	18	32	10	18	22	45
Complications (%)	9(18%) p < 0.01*	37(39%)	2(11%) NS	4(13%)	2(20%) NS	8(44%)	5(23%) p < 0.01	25(56%)
Septic complications	6(12%) NS	22(23%)	1(6%) NS	3(9%)	2(20%) NS	3(17%)	3(14%) p < 0.10	16(35%)
Major sepsis (%)	2(4%) p < 0.01	20(21%)	1(6%) NS	2(6%)	0 NS	3(17%)	1(5%) p < 0.05	15(33%)
Death (%)	2(4%) p < 0.005	27(28%)	0 NS	2(6%)	0 NS	4(22%)	2(9%) p < 0.01	21(47%)

\* p values via chi square—preoperative TPN vs no preoperative TPN.

mortality has not been objectively documented. Randomized controlled trials designed to evaluate the efficacy of this therapy are difficult because of the heterogeneity of the clinical population, multiple disease and treatment variables, and a strong bias among surgeons adversely effecting patient entry. Numerous studies have documented the feasibility and safety of preoperative and/or postoperative parenteral nutritional support as an adjunct to the surgical treatment of diseases of the head and neck,<sup>33</sup> esophagus,<sup>8,19,39</sup> stomach,<sup>11</sup> pancreaticobiliary system,<sup>11,20</sup> small- and large-bowel,<sup>11,29</sup> genitourinary system,<sup>3</sup> gynecologic system,<sup>18</sup> and various pediatric disorder.<sup>41</sup> Although these studies have demonstrated improved nutritional status in TPN-treated patients and low morbidity and mortality rates relative to historic or nonrandomized controls, few randomized prospective studies have been undertaken to objectively document the efficacy of perioperative parenteral nutrition in reducing operative morbidity and/or mortality. In a randomized, controlled study of 70 patients undergoing surgery for gastric cancer, Williams and co-workers<sup>40</sup> observed significantly fewer wound infections in patients who had received 7–10 days of preoperative nutritional support relative to unsupported controls. Although small differences in the incidence of other complications and death were noted between control and treated patients, these differences were not statistically significant. In a similar study Holter and co-workers<sup>21</sup> investigated the impact of parenteral nutritional support in 26 patients undergoing surgery for malignant disease of the gastrointestinal tract. Patients who had lost more than ten pounds preoperatively were entered into the study and were randomized

to receive hyperalimentation for 48 hours prior to surgery and ten days following surgery or to receive no parenteral nutritional support. Although patients on hyperalimentation lost less weight during the perioperative period, there was no difference in the postoperative complication rate between treated and untreated patients. The failure of parenteral nutrition to improve outcome in this study may not indicate that this is an ineffective modality. The period of preoperative nutritional support (48 hours) may have been insufficient to substantially reverse the catabolic state prior to surgery. Alternatively, the use of weight loss as a means of identifying which patients may benefit from nutritional support may be invalid. In previous studies from this institution<sup>5,30,31</sup> in which numerous measures of nutritional status were evaluated for their accuracy in predicting operative morbidity and mortality rates, only serum albumin, serum transferrin, delayed hypersensitivity and triceps skinfold were found to be useful. Although patients who suffered complications had lost more weight and had more rapid weight loss, these nutritional measures added no additional information in predicting operative morbidity. Other investigators have described a similar correlation between serum levels of proteins with relatively short half-lives,<sup>22</sup> delayed hypersensitivity,<sup>27</sup> and operative morbidity and mortality.

Results of the current study indicate that a period of adequate preoperative nutritional repletion of at least seven days is effective in reducing morbidity and mortality in a heterogeneous group of surgical patients. Patients were not randomly assigned to receive or not receive preoperative nutritional support. The decision to initiate support was based entirely on the clinical

impression of the patient's primary physician. For this reason the treated group (preoperative TPN) and the untreated group (no preoperative TPN) may not be strictly comparable, although the treated and untreated groups were virtually identical in terms of patient age, sex, underlying disease process, and nutritional status as measured by objective indicators (PNI).

In preoperative TPN-treated patients there was a two-fold reduction in complications ( $p < 0.01$ ) and a seven-fold reduction in deaths ( $p < 0.005$ ). The most dramatic decrease was noted in major septic complications (4 vs 21%;  $p < 0.01$ ), particularly the incidence of disseminated bacteremias (2 vs 13%  $p < 0.05$ ). No significant decrease in the incidence of minor septic complications (urinary tract infections, wound infections) were demonstrated although the incidence of these complications was small in both the treated and the untreated patients. The occurrence of these minor infections may reflect technical factors (indwelling Foley catheter, wound hematoma, contamination, etc) rather than host "susceptibility." The occurrence of major septic complications (bacteremia, intra-abdominal abscess, or pneumonia) may better reflect an inherent immunologic deficit within the host. The interrelationship between nutritional status and immunocompetence is complex and multifactorial. Malnutrition is clearly associated with an increased incidence of skin test anergy.<sup>27,30,32</sup> Abnormalities in serum immunoglobulin G, complement, lymphocyte count, lymphocyte response to phytohemagglutinin, and neutrophil chemotaxis have been described by Dionigi et al. in malnourished dogs.<sup>13</sup> These deficiencies may be corrected with nutritional repletion. Meakins and associates<sup>27</sup> studied the immune response in seriously ill, malnourished patients and demonstrated abnormalities of neutrophil chemotaxis, T-lymphocyte rosette formation, and lymphocyte chemotaxis<sup>6</sup> in anergic patients. The relative importance of nutritional and nonnutritional factors in giving rise to the immunologic deficits of patients who are both malnourished and seriously ill are not clear. The importance of nonnutritional factors has recently been demonstrated by Meakins et al.<sup>28</sup> in a series of anergic surgical patients. With no nutritional repletion, skin test reactivity was restored using Levamisole<sup>®</sup> producing a significant reduction in sepsis (16 vs 45%) relative to placebo-treated controls. The mechanism underlying this improvement in the immune response may be correction of the neutrophil chemotactic defect.<sup>7</sup> Nevertheless, Shizgal<sup>36</sup> and Spanier<sup>38</sup> have demonstrated that skin test anergy is closely correlated with an erosion of body cell mass (BCM).

Reconstitution of the BCM by total parenteral nutrition is frequently followed by restoration of skin test reactivity. Failure to restore the BCM despite adequate nutrition is associated with persistent skin test anergy and poor prognosis.

Fewer nonseptic complications were observed in patients who received preoperative nutritional support relative to untreated controls ( $p < 0.01$ ). The most marked decrease was noted in the incidence of acute respiratory failure which may reflect the impact of nutritional status on respiratory dynamics, particularly skeletal muscle function.

No inference regarding the efficacy of postoperative nutritional support in reducing operative morbidity and/or mortality rates may be drawn from this study. Virtually all patients (93%) received parenteral nutrition at some time during their hospital course. All patients who received preoperative support also received postoperative support beginning within the first 36 postoperative hours. In many patients who received only postoperative support, however, this was initiated only after the occurrence of an ultimately nonlethal complication and could not have influenced the development of that complication but may have influenced survival. The high mortality rate in this group may indicate that initiation of parenteral nutrition after the onset of a life-threatening complication is too late to "salvage" many patients. This finding is in agreement with Dietel and co-workers<sup>11</sup> who noted a 17% mortality rate in cancer patients treated with TPN after a life-threatening complication had occurred relative to no deaths in patients treated with preoperative and postoperative TPN.

Studies such as these emphasize the need to identify high risk patients *prior* to surgery. The importance of using objective measures of nutritional status in identifying these patients is demonstrated in this study. This study population represents a preselected population since all patients were referred to the Nutrition Support Service for nutritional assessment by their primary surgeon. Therefore, on clinical grounds there was a high index of suspicion that these patients would have nutritional deficits. In this population the mortality rate was 20% and the complication rate was 32% indicating the severity of their underlying disease. Based on clinical impression, 34% of these patients were considered to require preoperative nutritional support. However, when objective measures of admission nutritional status were retrospectively analyzed, virtually the same proportion of high risk (44 vs 47%) intermediate risk (20 vs 19%) and low risk (36 vs 34%) patients were found in the pre-

operatively supported group and the preoperatively unsupported group. The Prognostic Nutritional Index provides the clinician with an accurate and objective measure of operative risk in an individual patient. This "index" is a "nutritional composite" which includes measures of fat stores, secretory proteins, and immunocompetence, and in this preselected population further identified those patients that should have been considered candidates for preoperative support.

The Prognostic Nutritional Index permitted determination of the risk of nutritionally-based complications in these patients on an individual basis. Patients were classified as low risk, intermediate risk, or high risk on the basis of admission nutritional studies alone. Patients were not merely segregated on the basis of some nonnutritional factor such as age, sex, or underlying disease as shown by the similarity of these features in the three risk groups (Table 4). Among these patients who were subjectively considered to be at risk of significant nutritional deficits, 34% were classified as low risk and suffered a 12% complication rate and 4% mortality rate. Preoperative nutritional repletion was not effective in further reducing this minimal morbidity rate. Among patients classified by the PNI as intermediate risk there was a substantial reduction in complications, major sepsis, and death in TPN-treated patients, but no statistically significant differences could be demonstrated due to the small number of patients in this group. The most dramatic reduction in postoperative morbidity and mortality was observed in those patients identified as high risk on the basis of preoperative nutritional studies. In these patients, preoperative nutritional support produced a two and one-half-fold reduction in complications ( $p < 0.01$ ) a six-fold reduction in major sepsis ( $p < 0.005$ ) and a five-fold reduction in mortality ( $p < 0.01$ ). Despite this substantial reduction there was still a 23% complication rate and a 9% mortality rate in these high risk patients. This may indicate that TPN is ineffective in a subset of high risk patients, that certain complications are without a nutritional component, and/or that the duration of preoperative repletion was insufficient.

This study provides strong evidence that a previously developed and validated multiparameter prognostic nutritional index can identify a subset of operative candidates in whom preoperative nutritional repletion reduces operative morbidity and mortality. A well-controlled clinical trial is necessary for confirmation of these clinically and economically relevant findings.

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